73. (New) The soluble fusion protein of claim 8, wherein the gene VIII bacteriophage coat protein is about 40 to 50 amino acids in length.

REMARKS

As an initial matter, Applicants gratefully acknowledge withdrawal of rejections A-F under 35 USC §112, second paragraph.

Claims 1, 2, 4, 14, 18, 61, 65 and 67 have been amended to more particularly define the invention. Claims 68-73 have been added. Support for the amendments and new claims can be found throughout the subject application including the claims and drawings as filed originally.

Particular support for the amendment to claims 1, 14, 61 and 65 can be found in the specification at page 16, last paragraph, and pages 22-23, bridging paragraph (disclosing that a peptide linker sequence effectively positions the V-alpha and V-beta chains in an antigen binding pocket). Preferred methods for testing that binding are also disclosed. See e.g., the specification at pages 33-37 as well as the Examples.

Claims 1, 2, 4, 14, 18, 61, 65 and 67 have been amended to recite V-alpha and V-beta "regions" solely to comply with the Examiner's request that such terminology be used instead of V-"chains".

Claim 64 was further amended along lines requested by the Examiner at page 4 of the office action, except that the word "region" was used in place of "chain". Claim 65 was amended similarly.

Specific support for the new claims 68-73 can be found, e.g., at page 14, first full paragraph to page 16, first full paragraph (disclosing V-chains, C-chains, and bacteriophage coat proteins having preferred amino acid compositions).

The claim amendments and new claims do not introduce any new matter.

Claim 20 was rejected under 35 USC §112, first paragraph, on grounds that the specification does not enable human TCR sequences derived from the constant domain of the V-beta chain. Applicants respectfully disagree with this position.

The specification as filed fully complies with the "how to make" and "how to use" requirements of 35 USC §112, first paragraph.

For example, page 17 of the application discloses sources for DNA segments that encode human V-alpha and V-beta chains. As understood, the human V-beta chain includes the human C-beta chain, ie., as a V-beta/C-beta construct. Thus, the DNA segments provided would be recognized to encode the human C-beta chain as part of the V-beta chain. DNA segments from a variety of human cytotoxic T-cells (CTLs) are disclosed including naturally occurring and patient CTLs. Methods for making and using the CTLs to make the chains are taught, e.g., on page 17. More particular methods for making and using human patient CTLs are found in Example 18, for example. Illustrative methods for making the V-beta chains (with the C-beta domain) are discussed, e.g., at pages 18-19 and 21-42 of the specification.

Accordingly, it is submitted that the specification shows how to make and use the human C-beta chain which, as discussed, is understood to be part of the V-beta chain. Reconsideration and withdrawal of the rejection are therefor respectfully requested.

Claims 1, 2, 4, 14, 18, 61, 65 and 67 were rejected under 35 USC §112, second paragraph on grounds that "it is unclear what amino acid residues are encompassed by the claim language". See paragraph G at page 3 of the office action. Applicants disagree with the rejection. However the grounds for it are believed to be addressed by this submission.

In particular, claims 1, 14 and 65 have been amended to specify the V-alpha and V-beta regions more clearly. The amended claims point out that the *peptide linker sequence effectively positions the V-alpha and V-beta regions to form an antigen binding pocket*. One working in

this field would readily understand what V-regions are meant by claim. That is, the recited V-alpha and V-beta regions would be understood to be suitable for making an antigen binding pocket. Suitable V-chains for making the pocket are provided throughout the specification including page 14, first full paragraph. One working in the field would not need reference to particular amino acid sequences to understand what pocket forming V-regions are specified.

In view thereof, it is submitted that the claims as amended are clear and unambiguous to those working in the field. Reconsideration and withdrawal of the rejection are requested.

Claim 65 was rejected under 35 USC §112, second paragraph on grounds that the claimed fusion protein was unclear. Applicants disagree. However, to further prosecution, the claim has been amended along lines suggested by the Examiner in paragraph H. The word "region" has been used in place of "chain" to comply with the Examiner's request at paragraph 3 of the office action. Claim 64 has been amended along similar lines.

Claims 1, 2, 4, 6-8, 14, 18-20, 61, 65, and 67 were rejected under 35 USC §112, first paragraph on grounds that the claims are enabled only for fusion proteins comprising the C-beta region. Basis for the rejection has been addressed.

In particular, claims 1 as amended recites a soluble fusion protein that includes a C-β region fragment.

Applicants respectfully disagree with the rejection as to amended claims 14, 61 and 65. The fusion proteins featured in those claims are fully soluble.

Claims 1, 2, 4, 14, 18, 61, 65 and 67 were rejected as obvious in view of WO 96/18105 ("Strominger"), U.S. Pat. No. 5,759,817 ("Barbas"), Onda et al. (*Mol. Immunology* 32: 1387 (1995) "Onda"), and Huse et al. (*Immunol.* 149: 3914, (1992); "Huse"). The rejection is respectfully traversed.

Applicants submit herewith an executed Rule 131 Declaration ("Declaration") that effectively antedates the Strominger reference. Submission of the Declaration is proper because Strominger's 13 June 1996 publication date is less than one year prior to the March 17, 1997 filing date of the subject application.

The Declaration states that the inventors conceived and reduced the subject invention to practice in the United States well before Strominger's publication date. At paragraphs 5 and 7.

In particular, the Declaration states that there was recognition that recombinant TCR protein could be made in which V-alpha chain was covalently linked (fused) to V-beta C-beta chain by peptide linker sequence. At paragraph 6. The Declaration further states that it was recognized that bacteriophage coat protein could be fused to these chains to improve the TCR fusion protein. At paragraph 6.

The Declaration also states that vectors that encode the V-alpha chain fused to the V-beta C-beta chain and the bacteriophage coat protein were made well before Strominger's publication date. At paragraphs 8-13 (also referencing Figure 2 and Example 1 of the application).

Also stated is that the single-chain fusion protein was made (expressed) in the United States well before Strominger's publication date. At paragraph 14. In particular, the protein was made and subjected to purification well before that date. At paragraph 15.

In view thereof, it is submitted that grounds for the obviousness rejection have been traversed and the rejection should be withdrawn.

The cited portions of Barbas, Onda, and Huse, when taken individually or together, do not teach, suggest or provide any motivation to make or use the claimed invention.

More particularly, Barbas, Onda, and Huse, as relied on, do not teach or suggest Strominger's single-chain TCR molecules. Moreover, as cited, the references do not teach or

suggest characteristics of Strominger's single-chain TCR molecules as referenced at pages 5-6 of the office action.

In view of the discussion above, it is respectfully submitted that all rejections of record have been addressed. Early consideration and allowance of all the pending claims is earnestly solicited. The USPTO is hereby authorized to charge our deposit account no. 04-1105 for fees deemed to be necessary to consider this submission including the fee for new claims 68-73.

The office action dated June 23, 1998 indicated that PTO Form 948 (Notice of Draftsperson's Patent Drawing Review) was attached thereto. However, Applicants' representative has not received the PTO Form 948. The undersigned would be most grateful if the Examiner could forward that form in due course.

If the Examiner Lubet believes a telephone discussion would help further prosecution of this case, the undersigned would be grateful to have that discussion at the Examiner's convenience.

Respectfully submitted,

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